REMARKS

Claims 6 to 26 and 28 to 32 are pending. Claims 6-8, 25, 26, and 28-31 are currently under examination and stand rejected under 35 U.S.C § 103 as allegedly obvious over the combined teachings of the DOCK 4.0 User's Guide (1998) in further view of Takasaki et al. (Nature Biotechnology (1997) Vol. 15: pages 1266-1270) ("Takasaki") and Tang et al., (Chemistry and Biology (1997) Vol. 4, pages 453-459) ("Tang").

Applicants respectfully disagree that the cited references establish the *prima facie* obviousness of any of the previously pending claims. However, in the interest of advancing prosecution of this application, Applicants have amended the claims to more clearly define the claimed invention, and in the process further distinguish over the prior art.

In this regard, claims 26, 28, 29 and 30 have been amended to clarify that the allosteric cavity is *within about 15 to 20 angstroms* of the functionally critical site on the target protein. Support for this amendment may be found in the application as filed, for example, at page 9, line 10. The claims have also been amended to clarify that the allosteric modulator is a *small molecule*. Support for this amendment is obtained throughout the specification. For example, all of the compounds identified in the Formulae on pages 40 to 81 (and further described in the text) are small molecules. Further support may be found, for example, at page 19, lines 3 to 12, where the advantages of using the three-dimensional structure chemical database of small molecules is discussed. No new matter is added.

Rejection Under 35 U.S.C. § 103

Applicants respectfully submit that amended claims clearly define over the three references cited in the Office Action dated November 7, 2008.

The claims are directed to methods of identifying *allosteric* modulators of intermolecular interactions between a protein and a modifier. As the Examiner will understand, the term "allosteric modulator" in this context means a compound that will act on a protein at a site that is *apart from* the site that is critical to the functionally critical site involved in the intermolecular interaction. More specifically, as amended herein, the claims specify that the allosteric modulator is a *small molecule compound* that contain at least one functional group that can be

accommodated by an allosteric cavity that is *within 15 to 20 angstroms* from the functionally critical site. Through practice of the claimed methods, small molecule compounds may be identified that will interact with the target protein at the allosteric site, and as a result modulate the intermolecular interaction that may occur between the target protein and a modifier at the nearby (*i.e.*, within about 15-20 angstroms) functionally critical site.. Importantly, these methods allow the identification, for example, of small molecules that *non-competitively* inhibit various protein-protein interactions.

Applicants respectfully submit that the claimed methods are neither taught nor suggested by any proper combination of the DOCK User's Guide, Takasaki and Tang. The DOCK User's Guide completely fails to mention any allosteric cavity, or provide even the slightest suggestion as to how one might go about identifying a cavity that, if accommodated by a small molecule compound, would modulate intermolecular interactions at a functionally critical site. There is certainly no suggestion that a cavity that is located within 15-20 angstroms should be selected. Indeed, there is nothing in the DOCK User's Guide that even suggests allosteric modulation may be possible. Thus, while the DOCK program may be useful in identifying small molecules that have the potential to interact within a given protein cavity, there is nothing in the User's Guide that would lead one of ordinary skill in the art to select any particular cavity from among the thousands of cavities that may be present in a target protein, and nothing to suggest that binding of a compound within any of those cavities would produce an allosteric effect on the functionally critical site on the protein.

The Takasaki reference does nothing to overcome these deficiencies. As noted in Applicants' prior response, the Takasaki reference does not teach or suggest identifying an allosteric site on the receptor. Rather, Takasaki relates to interactions that occur at one of the critical sites –WP9– on the TNF receptor where its ligand TNFα binds. Specifically, they designed peptidomimetics having a similar shape to this critical site and an anti-TNFα monoclonal antibody, which would have the ability to bind TNFα, and tested whether the peptidometic prevented TNFα binding and activation of the receptor. Thus, while the Takasaki reference may describe the identification of critical binding sites within the TNF receptor, it says

nothing about *allosteric modulation* of such a site. Thus, there is nothing in this reference that, when combined with the DOCK User's Guide, would suggest the methods of the present invention.

The Tang reference also does nothing to overcome the deficiencies of the two other references. At most, Tang would suggest to those of skill in the are that allosteric regulation of protein enzymes by ribosomes is known, and that it may be possible to "engineer" the ribosomes in a way that would influence the efficacy of this regulation. This has nothing to do with the methods of the present invention, however. In particular, Tang is directed exclusively to *ribosomal* constructs, and there is absolutely nothing in the reference that would teach or suggest the identification of *small molecule* compounds suitable for use in allosteric modulation of intermolecular interactions. Further, Tang contains no teaching or suggestion of how a cavity on a protein may be selected that would be suitable for inducing an allosteric effect, much less how one would develop information that would be useful for selecting molecules that may interact with such cavities. As such, there is nothing in the Tang reference that could be combined with the Dock User's Guide and/or Takasaki to lead one to the claimed invention.

Applicants submit, therefore that no proper combination of the three cited references in any way establishes the *prima facie* obviousness of the claimed invention. There is simply nothing in the combined teachings that suggest a method for identifying small molecule modulators that includes, *inter alia*, the steps of identifying an allosteric cavity that is within 15 to 20 angstroms of a functionally critical site, calculating the dimensions and mapping the chemical and/or electrostatic properties of said cavity, and utilizing this information to identify small molecule compounds containing at least one functional group that can be accommodated by said cavity.

In addition, Applicants note that there is further nothing in any of the cited art that would lead one of ordinary skill in the art to use nuclear magnetic resonance, crystal structure analysis, calorimetric values from thermodynamic studies or computer modeling (as recited in claim 25), in addition to distance from a functionally critical site, to determine which of the thousands of cavities that may be present within a given target protein should be identified as a cavity that is

likely to induce an allosteric effect. Similarly, the Office has failed to identify any prior art that teaches or suggests the use of thermal β-factors, as recited in claim 31, to identify a cavity that is suitable for exploration as a site for inducing allosteric modulation. Thus, the Office has failed to indicate how these additional claim elements are rendered obvious by the prior art.

Conclusion

For these reasons, Applicants respectfully submit that the pending claims, as amended herein, are nonobvious over the references cited in the Office Action. Applicants request, therefore, that the allowability of claims 6-8, 25, 26, and 28-31 be acknowledged. Withdrawal of the pending rejections, rejoinder and favorable consideration of the withdrawn claims, and an early notice of allowance of all of pending claims 6 to 26 and 28 to 32 are earnestly solicited.

In the event the Examiner is of the opinion that any of the claims are not allowable, Applicants respectfully request the courtesy of a telephone call to their undersigned representative, so that an interview may be conducted prior to issuance of a further action.

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